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An Enantiospecific Synthesis of (+)-Methyl Epijasmonate and (-)-Methyl Cucurbate from L-Glutamic acid

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Abstract: An enantiospecific route to jasmonoid natural products, (+) - methyl epijasmonate and (-) -methyl cucurbate from L-glutamic acid is reported. The key step is a 5-(3,4) ene cyclization of a functionalized 1,6-diene as chiron, which sets up three chiral centres with a high degree of diastereoselectivity. © 1998 Elsevier Science Ltd. All rights reserved.

Introduction

Recently, we have reported an intramolecular ene-based methodology for the stereocontrolled construction of 1,2-disubstituted and 1,2,3-trisubstituted cyclopentanes.¹ This synthesis allows introduction of a versatile allylsilane side chain which can be exploited for further elaboration of the ring systems. Herein, we wish to report the first 'chiral pool' synthesis of (+)-methyl epijasmonate (1) and (-)-methyl cucurbate (2) using this ene cyclization as the key step.² Methyl epijasmonate 1³ and its analogs, methyl tuberonate 3,⁴ β -D-glucopyranosyltuberonic acid 4⁴ and its methyl ester 5⁴ as well as cucurbic acid 6⁵ have remarkable bioactivities, such as strong jasmine note,^{3a,b,c} pheromone synergest,^{3b,c} potato-tuber induction⁴ and plant growth regulation.⁵ In view of their numerous biological activities, jasmonoids including 1 and 2 have been the targets of many synthetic efforts, and recently various enantioselective synthesis of these molecules have appeared in the literature.⁶



Results and Discussion

As shown in Scheme 1, our retrosynthetic analysis involves the 5-(3,4) ene cyclization of chiron 8 to the 1,2,3-trisubstituted cyclopentane derivative 7 containing an allylorganometallic side chain. Chiron 8 should be available from L-glutamic acid 10 via the α -alkoxy aldehyde 9 by usual synthetic methodology.





Scheme 2



a) DIBAL-H,THF,-78°C, 1h, Ph₃P=CHCO₂Me, -78°C \rightarrow r.t., 5h,80%. b) *t* -BuPh₂SiCl, Im, DMF, r.t., 12h, 55%. c) PPTS, EtOH, r.t., 89%. d) DMSO, (COCl)₂, Et₃N, - 60°C \rightarrow r.t., 96%. e) Ph₃(CH₂CH₂CH₂TMS)PBr, NaN(TMS)₂, THF, - 78°C \rightarrow r.t., 71%. f) 235°C, 18h, 95%. g) HI, bz, r.t., 78%. h) O₃, - 78°C, 1h, then Me₂S, 88%. i) Ph₃(Pr)PBr, NaN(TMS)₂, THF, - 78°C \rightarrow r.t., 1h, 50%. j) n-Bu₄NF, THF, r.t., 84%. k) H₂CrO₄, ether, 0°C, 20min, 69%.

Putting this plan to action, the known lactone 11,⁷ readily made from L-glutamic acid, was transformed to 12 in one-pot⁸ by reduction with DIBAL-H followed by the addition of the necessary phosphorane (Ph₃PCHCO₂Me) in 80% yield and 95% *ee* (Scheme 2). The enantiomeric excess was determined by preparing Mosher esters⁹ with both (R)-(+)-MTPA and (S)-(-)-MTPA and ¹⁹F-NMR analysis of the diastereomers. With 12 in hand, attempts were made to transform it to the silylether 13 by exposure to TBDPS-Cl / Im at ambient temperature. However, under the usual conditions, an exchange product, e.g., 15 (20-30%) always accompanied the desired product 13. This type of migration is not, however, uncommon in the literature.¹⁰ Modified conditions were soon worked out by mixing the reagents at a low temperature (-30⁰C) and then slowly warming up to room temperature and this minimized the by-product 15 (~5%) so as to increase the yield of 13 to a respectable 55%. Selective mono-desilylation¹¹ using PPTS in MeOH was uneventful and 14 was obtained in very high yield (89%). It may be mentioned here that formation of 15 during the conversion 12->13 was actually confirmed by selective monodesilylation of 15 to 16 and analysis of its ¹H-NMR. For example, while the olefinic and allylic protons in 16 appear at lower fields, C₆ -H actually resonates at a higher field when compared to similar protons of 14.

Swern oxidation of 14 afforded the α -silvloxy aldehyde 18 in 96% yield which without further purification was immediately subjected to Bestmann-Wittig¹² olefination (using Ph₃(TMSCH₂CH₂CH₂) PBr/NaN(TMS)₂) in THF to ultimately deliver the chiron 19 (E/Z=16/84) in 71% yield. Nonetheless, these last two steps warrant some in-depth discussion. α -Alkoxy aldehydes are generally labile and there are several cases reported in the literature¹³ where oxidation of carbinols leading to α -alkoxy aldehydes were complicated by facile epimerization at the α -centre and consequent racemization. This is the reason why crude aldehyde 18 was promptly subjected to Wittig-olefination (18-19) under salt-free conditions. Considerable experimental efforts were expended to find a suitable condition for the olefination step $(18 \rightarrow 19)$, though, which proved very frustrating in the beginning as the yield was very poor (10-20%) and E/Z ratio also varied from batch to batch. That an α -alkoxy substituent on aldehydes and ketones can result in abnormal Wittig reaction stereochemistry, depending on experimental conditions, is well-docummented and this area has recently been reviewed by Marvanoff.¹⁴ In some runs, formation of 7E-19 and 7Z-19 in even 1:1 ratio was also observed, especially when the phosphonium salt (Ph₃(TMSCH₂CH₂CH₂)PBr) and NaN(TMS)₂ were allowed to stir at room temperature in THF for about an hour for completion of ylide formation. It may be mentioned here that the above experimental condition work very well with ordinary aldehydes for high-yield synthesis of Z-olefins as reported earlier from this laboratory.^{1c} Later it was found that the ylide, Ph₃PCHCH₂CH₂TMS, has to be added within 10 mins of its preparation to the aldehyde 18 whereby the yield (71%) as well as stereoselectivity (E/Z=16/84) improved dramatically. The reason for this improvement is not clear to us at present.

The remaining steps of the synthesis are as described previously for the racemic series.² Thus, heating a 5% solution of 19 in toluene in a sealed tube under argon at 235°C for 18h smoothly effected carbocyclization to a mixture of allylsilanes 20 and 21 in a ratio of 90:10 in 95% yield.

In order to rationalize the high stereoselectivities observed in the present ene cyclization, the Oppolzer model¹⁵ of transition states is invoked as the Houk model¹⁶ is inadequate in the case of activated enophiles. The exclusive formation of *E*-allylsilanes 20 and 21 from *Z*-19 is accountable in terms of relevant transition states, namely A which is favoured over C due to 1,3- diaxial interaction. The transition state A is more stable than B as the alkoxy group in B is endo and this explains the formation of the minor diastereomer 21. The other transition state e.g., D leading to the 1,2-*trans* disubstituted product is discarded due to obvious angle strain reasons.



In the case of cyclization of E-19, the steric interactions are relatively subtle and, therefore, diastereoselection and diastereofacial selection are expected to be only low to moderate on the basis of Nakai's pinoneering work.¹⁷ The two transition states E and F are, respectively, equally likely from (E)-19 leading to 20 and 27. However, based on our experimental results it seems that contribution from TS-F is minimal at best.

To determine the extent of internal asymmetric induction in the ene cyclization step, 20 and 21 were protodesilylated (with HI) and the products 22, 23 subjected to desilylation (with n-Bu4NF) to give 24 which has an ee of 87% as determined by Mosher ester analysis.⁹ Unfortunately, the conversion of 12 to 20 and 21 was unavoidably accompanied with some racemization. Probably, partial racemization occurs at the aldehyde 18 stage during Swern oxidation. Oxidative cleavage (with O_3) of the protodesilylated products 22, 23 gave the jasmonoid building block 25 (88%) (only one diastereomer is shown henceforth for convenience). Wittig olefination (50%) under salt-free condition,¹² followed by exposure of the product to n-Bu₄NF gave (-)-methyl cucurbate (2) in 84% yield and ca. 87% ee. During the later step, the minor C₃- β isomer (~ 10%) carried over from 20 / 21 was eliminated presumably via a lactone.² The optical rotation $[\alpha]_{D}$ = -2.03 (C=1.12 in MeOH) of 2 agreed with literature 6c value ($[\alpha]_D = -2.20$, C = 0.22 in MeOH). Incidentally, saponification of 2 with KOH in aqueous MeOH at 50°C gave (+) - cucurbic acid 6 in 98% yield (~ 87% ee). The optical rotation of 6, $[\alpha]_{\rm D}$ = +20.29 (C= 0.32 in MeOH) also agreed with those reported in the literature⁵ for natural cucurbic acid $([\alpha]_{D} = +25, C = 0.36$ in MeOH). Finally oxidation with chromic acid under Brown's condition¹⁸ yielded (+)methyl epijasmonate (1) (87% ee) in 69% yield (5% overall yield from 11). The synthetic (+)-methyl epijasmonate 1 has a very intense, typical "jasmonte fragrance". Furthermore, since modified working conditions were used in Brown oxidation step, our synthetic (+)-1 seems to be free from its C-2 epimer (methyl jasmonate). The optical rotation $[\alpha]_D = +50.4$ (C= 0.96 in MeOH) of 1 agreed with the literature⁶ value $([\alpha]_D = +53.3, C = 0.98 \text{ in MeOH}).$

Having developed a new synthetic route to the chiral jasmonoid building block 25, it was of interest to channelize the same to methyl tuberonate (3) and congeners 4, 5. Unfortunately, in our hands, exposure of 25 to the ylide $Ph_3PCH(CH_2)_2OTMS$ (29)¹⁹ has thus far failed to give even traces of 30, precursor for tuberonates.

In summary, we have developed a new enantio- and diastereoselective synthesis of jasmonoids using 5-(3,4) ene cyclization as the key step and our synthesis now joins four other^{6c,f,g,h} enantioselective syntheses of 1 and/or 2.

EXPERIMENTAL

(S)-Methyl (2E)-6-hydroxy-7-(*tert*-butyldimethylsilyloxy)-2-heptenoate (12): To a well stirred solution of 11(2 g, 8.7 mmol) in 25 mL THF was added a 1.5(M) solution of DIBAL-H in hexane (6.37 mL, 9.56 mmol) over 1.5 h. During the addition the temperature was kept below -68° C. After an additional 30 min, the solution of carbomethoxymethylenetriphenylphosphorane (3.48 g, 10.4 mmol) in 25 mL of dichloromethane was added to the stirred solution at -78° C. The mixture was stirred for 1 h at -78° C and then slowly brought to room temperature. The mixture was quenched with water and extracted with dichloromethane. The combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated. Column chromatography of the crude product on silica gel and elution with ethyl acetate-petroleum ether (60-80°C) (1:9) gave 12 (2 g, 80%)

as a colourless oil. $[\alpha]_D = -7.3$ (C= 1.00 in MeOH); IR (film) v_{max} : 3471, 2943, 2861, 1720, 1654, 1442, 1168, 841, 777 cm⁻¹; ¹H-NMR (200 MHz, CDCl₃): δ 6.97 (dt, 1H, 15.6 & 6.8Hz), 5.84 (dt, 1H, 15.6 & 1.5Hz), 3.68 (s, 3H), 3.69-3.57 (m, 2H), 3.44-3.35 (m, 1H), 2.43-2.45 (m, 2H), 2.06 (bs, 1H), 1.61-1.48 (m, 2H), 0.89 (s, 9H); ¹³C-NMR(50 MHz, CDCl₃): δ 167.0 (s), 148.9 (d), 121.0 (d), 70.9 (d), 67.0 (t), 51.3 (q), 31.1 (t), 28.3 (t), 25.8 (q), 18.2 (s), -5.38 (q), -5.43 (q). Anal.Calcd. for C₁₄ H₂₈ O₄Si : C, 58.29; H, 9.78; Found: C, 58.33; H, 9.81.

Determination of the enantiomaric purity of 12. 12 was converted into corresponding (R)- and (S)-MTPA esters 17 in the usual manner. Both the diastereomers were analysed by ¹⁹ F-NMR (400 MHz). The CF₃ signals of the two diastereomers appear at δ 60.9 and 61.0 and from their relative integral values, the *ee* of 12 was readily determined to be about 95%.

(S)-Methyl(2E)-6-(*tert*-butyldiphenylsilyloxy)-7-(*tert*-butyldimethylsilyloxy)-2-heptenoate (13) : To a solution of 12 (5 g, 17.3 mmol) and imidazole (4.81 g, 70 mmol) in dimethylformamide (37mL) was added *tert*-butyldiphenylchlorosilane (5.2 g, 19mmol) under argon at -30° C. The mixture was slowly warmed to room temperature and stirred for 10h. The mixture was poured into water (130mL) and extracted with ether (5 x 40mL). The combined ether extracts were washed with water, brine, dried (MgSO₄) and concentrated. Column chromatography of the residue on silica gel and elution with ethyl acetate petroleum ether (60 -80°C) (3:97) gave a colourless thick oil 13 (5.5 g, 55%). [α]_D = +1.06 (C=1.03 in CH₂Cl₂). IR (film)v_{max}: 2938, 2860 1726, 1656, 1452, 1106, 703 cm⁻¹; ¹H-NMR (200 MHz ,CDCl₃): δ 7.69 - 7.63 (m, 4H), 7.43- 7.31 (m, 6H), 6.88 (dt, 1H, J = 15.6 & 6.8Hz), 5.79 (dt, 1H, J = 15.6 & 1.6Hz), 3.75-3.71 (m, 1H), 3.71 (s, 3H), 3.51-3.35 (m, 2H), 2.24-2.17 (m, 2H), 1.71-1.58 (m, 2H), 1.05 (s, 9H), 0.80 (s, 9H), -0.08 (s, 3H), -0.11 (s, 3H); ¹³C-NMR (50 MHz, CDCl₃): δ 166.7 (s), 149.4 (d), 135.8 (d), 135.6 (d) , 134.2 (s), 134.0 (s), 129.7 (d), 129.6 (d), 127.7 (d), 127.6 (d), 120.9 (d), 72.8 (d), 65.9 (t), 51.2 (q), 32.1 (t), 27.3 (t) 27.0 (q), 25.95 (q), 19.43 (s), -5.4 (q).

(S) -Methyl (2*E*) -7-hydroxy-6- (*tert*-butyldiphenylsilyloxy)-2- heptenoate(14): To a solution of 13 (5.59 g, 11 mmol) in methanol (150ml) was added pyridinium p-toluene-4-sulphonate (461 mg) and the mixture was stirred for 24h. Removal of the solvent in vacuo followed by chromatography of the residue on silica gel and elution with 20% ethyl acetate - petroleum ether ($60-80^{\circ}C$) gave 14 as a colourless thick oil (3.9 g, 89%). IR (film)v_{max}: 3423, 2931, 1720, 1650, 1428, 1056, 822, 738 cm⁻¹; ¹H -NMR (200 MHz, CDCl₃): δ 7.70 -7.63 (m, 4H), 7.44-7.34 (m, 6H), 6.76 (dt, 1H, J= 15.6 & 6.83Hz), 5.66 (dt, 1H, J= 15.6, 1.45Hz), 3.70 (s, 3H), 3.78 -3.72 (m, 1H), 3.6 -3.49 (m, 2H), 2.13-2.06 (m, 2H), 1.69-1.56 (m, 2H), 1.07 (s, 9H); ¹³C-NMR (50 MHz, CDCl₃): δ 166.7 (s), 148.6 (d), 135.8 (d) 135.6 (d), 133.7 (s), 133.4 (s), 129.9 (d), 127.7 (d), 127.7 (d), 121.0 (d), 73.2 (d), 65.7 (t), 51.2 (q), 31.8 (t), 27.7 (t), 27.0 (q), 19.2 (s).

(S)-Methyl (2E) -6- hydroxy -7- (tert-butyldiphenylsilyloxy -2- heptenoate (16):

a) To a solution of 12 (500 mg, 1.7 mmol) and imidazole (0.4 g, 5.8 mmol) in dimethylformamide (5mL) was added *tert*-butyldiphenylchlorosilane (0.5 g, 2 mmol) under argon at room temperature and stirred for 10h. The mixture was poured into water (10mL) and extracted with ether (5 x 4mL). The combined ether extracts were washed with water, brine, dried (MgSO₄) and concentrated. Column chromatography of the residue on silica gel and elution with ethyl acetate-petroleum ether (60 - 80° C) (3:97) gave a mixture of 13 and 15 as a colourless oil (200mg).

b) The oil as obtained above was selectively deproctected following the procedure as described for 14 to give 14 (110mg) as major product and 16 (80 mg) as minor product. IR (film) v_{max} : 3426, 3070, 2928, 2860, 1720, 1450, 1060, 738 cm⁻¹; ¹HNMR (200 MHz, CDCl₃): δ 7.65 - 7.61 (m, 4H), 7.43 - 7.33 (m, 6H), 6.93 (dt, 1H, J = 15.6 & 6.88Hz), 5.79 (dt, 1H, J = 15.6 & 1.4Hz), 3.71 (s, 3H), 3.68 - 3.60 (m, 2H), 3.51-3.42 (m, 1H), 2.41 -2.22 (m, 2H), 1.63 -1.5 (m, 2H), 1.06 (s, 9H).

(S)-Methyl (2E)-7-0x0-6-(*tert*- butyldiphenylsilyloxy) -2- heptenoate(18): To a solution of oxalyl chloride (0.73 mL, 7.5 mmol) in dichloromethane (20 mL) at - 60° C was added dropwise with stirring a solution of dimethyl sulfoxide (1 mL) in dichloromethane (25 mL) under an atmosphere of argon over a period of 20 min. To this, after stirring for 15min, 14 (2.7 g, 6.3 mmol) was added in dichloromethane (10 mL) over a period of 15 min. Stirring was continued for an additional 30 min and triethylamine (4.7mL) was added at the same temperature. After 10 min the reaction mixture was allowed to attain room temperature, diluted with water (25 mL) and the aqueous phase extracted with dichloromethane (3 x 15 mL). The organic phase was washed with brine, dried (MgSO₄) and concentrated. The residue was passed through a short bed of silica gel and elution with ethyl acetate - petroleum ether (60 - 80°C) (1:9) gave 18 (2.5g, 93%) as an oil. IR (film)v_{max}: 3063, 2929, 2858, 1726, 1653, 1553, 1475, 1334, 1178, 1098, 711 cm⁻¹; ¹H-NMR (200 MHz, CDCl₃): δ 9.59 (s, 1H), 7.64-7.59 (m, 4H), 7.41-7.38 (m, 6H), 6.81(dt, 1H, J = 15.6 & 6.8Hz), 5.6 (dt, 1H, J = 15.6 & 1.5Hz), 4.2-4 (m, 1H), 3.70 (s, 3H), 2.2-2.3 (m, 2H), 1.88-1.7 (m, 2H), 1.11 (s, 9H).

(S) -Methyl (2E,7Z) -10- (trimethylsilyl)-6-(*tert*-butyldiphenylsilyloxy) -2, 7 - decadienoate (19): To a mixture of 3- (trimethylsilyl)-propyltriphenylphosphonium bromide^{1c} (12.5 g, 27.4 mmol) and sodium hexamethyldisilazide (4.8 g, 26.2 mmol) was added dry THF (50mL) using a hypodermic syringe under an atmosphere of argon. The reaction mixture was stirred for 10 min, during this period the reaction mixture developed a bright orange colour indicating the formation of the ylide. This was added to a solution of 18 (2.5 g, 6.0 mmol) at -78^oC, the resulting mixture stirred for 1h and then slowly brought to room temperature. This was diluted with petroleum ether (60-80^oC) and the precipitated triphenylphosphine oxide separated by filtration. The filtrate was concentrated and the residue passed through a bed of silica gel. The crude oil, thereby, obtained was chromatographed over silica gel and eluted with ethyl acetate-petroleum ether (60 - 80^oC)) (3 : 97) to give 19 (*E/Z* = 16:84) as a colourless thick oil (2.2 g, 71%). [α]_D = +20.9 (C = 0.876 in MeOH); IR (film) v_{max} : 2942, 1724, 1654, 1442, 1266, 1182, 1080, 842, 705 cm⁻¹; ¹H -NMR (200 MHz, CDCl₃): δ 7.75 -7.63 (m, 4H), 7.5-7.3 (m, 6H), 6.88 (dt, 1H, J= 15 & 8Hz), 5.68 (d, 1H, J= 15Hz), 5.4 -5.20 (m, 2H), 4.44 -4.34 (m, 1H), 3.70 (s, 3H), 2.2 -2.07 (m, 2H), 1.7 - 1.46 (m, 4H), 1.03 (s, 9H), 0.35 -0.23 (m, 2H), -0.037 (s, 9H, from 7 *E* isomer), - 0.133 (s, 9H); ¹³C-NMR (200 MHz, CDCl₃): δ 166.98 (s), 149.35 (d), 135.99 (d), 135.84 (d), 134.26 (s), 134.14 (s), 133. 52 (d), 130.60 (d), 129.60 (d), 129.45 (d), 127.55 (d), 127.35 (d), 120.81 (d), 68.68 (d), 51.28 (q), 36.64 (t), 27.68 (t), 27.00 (q), 21.85 (t), 19.27 (s), 16.72 (t), -1.85 (q); ¹³C-NMR (partial) for 7*E* -19 - isomer: δ 149.54 (d), 73.83 (d), 36.24 (t), 26.29 (t), 15.92 (t), -1.70 (q); Anal. Calcd. for C₃₀ H₄₄ O₃Si₂: C, 70.82; H, 8.71; Found: C, 70.95; H, 8.74.

Methyl (1R, 2S, 3S) - 2 - [2 - [(E) - 3 - (trimethylsilyl)-1- propenyl] -3- (tert-butyldiphenylsilyloxy) cyclopentyl] acetate (20) and Methyl (1S,2R, 3S) - 2 - [2 - [(E) - 3 - (trimethylsilyl) - 1 - propenyl] -3 -(tert-butyldiphenylsilyloxy) - cyclopentyl [acetate (21): A solution of 19 (1.4 g, 2.9 mmol) in dry toluene (30mL) was taken in 7 corning tubes (30 cm long, 2cm diameter), purged with argon and sealed. These sample tubes were heated at $235^{\circ}C$ ($\pm 2^{\circ}C$) for 18h in a constant temperature oven. After cooling to room temperature, the solvent was removed in vacuo and preparative layer chromatography [silica gel, 2.5% ethyl acetate- petroleum ether ($60 - 80^{\circ}$ C) as developing solvent] of the residue gave 20 and 21 (1.33 g, 95%) as a colourless thick oil. [α]_D = -17.108 (C=1.66 in MeOH); IR (film)v_{max}: 3050, 2942, 1738, 1624, 1440, 1258, 1168, 1092, 842, 704 cm⁻¹; ¹H-NMR for major isomer 20 (200 MHz, CDCl₃): δ 7.65 - 7.61 (m, 4H), 7.41 -7.32 (m, 6H), 5.13 (dd, 1H, J=15 & 8Hz), 4.73 (dd, 1H, J = 15 & 10Hz), 4.00 -3.99 (m, 1H), 3.65 (s, 3H), 2.79 - 2.69 (m, 1H), 2.52 (t, 1H, J = 8Hz), 2.29 (dd, 1H, J= 15.5 & 6.7Hz), 2.14 (dd, 1H, J= 15.5 and 8.7Hz), 1.99 -1.92 (m, 1H), 1.86 -1.78 (m, 1H), 1.66 -1.59 (m, 1H), 1.29 (d, 2H, J = 8Hz), 1.25 -1.17 (m, 1H), 1.07 (s, 9H), -0.07 (s, 9H). ¹H-NMR for other minor diastereomer 21 (partial): δ 5.36 -5.34 (m, 2H), 4.21 - 4.15 (m, 1H), 3.63 (s, 3H), 2.4 - 2.22 (m, 2H), 1.03 (s, 9H), 0.02 (s, 9H); ¹³C-NMR for major isomer 20 (50 MHz, CDCl₃): δ 173. 48 (s), 135.94 (d), 135.82 (d), 134.69 (s), 134.50 (s), 129.48 (d), 129.17 (d), 127.54 (d), 125. 64 (d), 80.39 (d) 55.54 (d), 51.21 (q), 37.07 (d), 36.36 (t), 33.43 (t), 28.58 (t), 27.19 (q), 23. 23 (t) 19.28 (s), -1.77 (q); ¹³C-NMR for other minor diastereomer 21: δ 124.86 (d), 77.18 (d), 50.11, 35.40, 32.62 (t), 29. 79, 28.32; Anal. Calcd. for C₃₀ H₄₄ O₃ Si₂: C, 70.82; H, 8.71; Found: C 70.91; H, 8.75.

Methyl (1R,2S, 3S) - 2-[2-(2-propenyl) -3-(*tert* -butyldiphenylsilyloxy)cyclopentyl acetate (22) Methyl (1S,2R, 3S) - 2-[2-(2-propenyl) -3-(*tert* -butyldiphenylsilyloxy)cyclopentyl acetate (23): To a stirred solution of 20 and 21 (450 mg, 0.8 mmol) in dry benzene (12 mL) was added 57% aqueous hydrogen iodide (0.1 μ L) and stirred for 12h at room temperature. The organic layer was washed with water (2 x 15 mL), brine, dried (Na₂SO₄) and concentrated. Preparative layer chromatography [silia gel, 2% ethyl acetate petroleum ether (60 - 80°C) as developing solvent] of the residue gave 22, 23 (300 mg, 78%) as a colourless thick oil. [α]_D = + 5.15 (C = 0.35 in MeOH); IR (film) ν_{max} : 3056, 2942, 1736, 1642, 1444, 1362, 1268, 1174, 1090, 914, 826, 706 cm⁻¹, ¹H -NMR (200 MHz, CDCl₃): δ 7.75-7.62 (m, 4H). 7.48-7.32 (m, 6H), 5.53 - 5.27 (m, 1H), 4.90-4.75 (m, 2H), 4.08-3.98 (m, 1H), 3.65 (s, 3H), 2.92-2.7 (m, 1H), 2.24 (dd, 1H, J=15.09 & 6.4 Hz), 1.98 (dd, 1H, J= 15.09 & 9.4Hz), 2.1-1.55 (m, 6H), 1.33-1.14 (m, 1H), 1.05 (s, 9H); ¹H NMR for other minor diastereomer **23**: δ 4.28-4.18 (m, 1H), 3.66 (s, 3H), 2.62 -2.52 (m, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 173.78 (s), 137.08 (d), 135. 85 (d), 134.62 (s), 134.38 (s), 129.45 (d), 127.47 (d), 115.48 (t), 78.18 (d), 51.42 (q), 50.05 (d), 36.15 (d), 35.42 (t), 32.51 (t), 31.470 (t), 28.18 (t), 27.01 (3q), 19.13 (s); Anal. Calcd. for C₂₇H₃₆O₃ Si: C, 74.27; H, 8. 31; Found: C, 74.77; H, 8.35.

Methyl (1R, 2S, 3S) -2-[2-[2-propenyl] -3- hydroxycyclopentyl Jacetate (24): To a solution of 22 and 23 (67 mg, 0.15 mmol) in tetrahydrofuran (5mL) was added tetrabutylammonuim fluoride trihydrate (96 mg, 0.307 mmol) under an argon atmosphere. After being stirred for 24h at room temperature, the mixture was partitioned between ether and saturated aqueous sodium chloride, and the aqueous layer was extracted with ether (4 x 5 mL). The combined ether extracts were dried (MgSO₄) and concentrated in vacuo. Preparative layer chromatography [silica gel, 15% ethyl acetate- petroleum ether (60 - 80^o C) as developing solvent] of the residue afforded 24 (25 mg, 83 %) as a colourless oil. $[\alpha]_D = + 4.43$ (C= 0.29 in MeOH); IR (film)v_{max}: 3430, 2970, 1735, 1643, 1444, 1310, 1250, 810, 600 cm ⁻¹; ¹H-NMR (200 MHz, CDCl₃): δ 5.88-5.75 (m, 1H), 5.10-5.01 (m, 2H), 4.05 - 3.98 (m, 1H), 3.66 (s, 3H), 2.69-2.62 (m, 1H), 2.41 (dd, 1H, J= 15.09 & 6.2 Hz), 2.17 (dd, 1H, J= 15.09 & 9.4Hz), 2.09 - 1.6 (m, 6H), 1.35 - 1.00 (m, 1H); ¹³C-NMR (50 MHz, CDCl₃): δ 173. 6 (s), 137.2 (d), 116.1 (t), 77.31 (d), 51.5 (q), 49.7 (d), 36.42 (d), 35.16 (t), 32.45 (t), 29.59 (t), 28.3 (t).

Determination of the enantiomaric purity of 24. 24 was converted into corresponding (R)- and (S)-MTPA esters **28** in the usual manner. Both the diastereomers were analysed by ¹⁹ F-NMR (400 MHz). The CF₃ signals of the two diastereomers appear at $\delta 60.9$ and 60.78 and from their relative integral values, the *ee* of **24** was readily determined to be about 87%.

Methyl-(1R, 2S, 3S) -2-[2-(2-oxo -Methyl)-3- (*tert*-butyldiphenylsilyloxy)cyclopentyl]- acetate (25): Ozone was bubbled through a solution of 22 and 23 (265 mg, 0.6 mmol) in methanol (20 mL) at -78° C till the blue colour persisted for more than 10min. The excess ozone was removed by allowing nitrogen gas to bubble through the solution at -78° C. Dimethyl sulfide (3 mL) was added dropwise at the same temperature. The mixture was allowed to attain room temperature and stirred for 2h. Excess dimethyl sulfide was removed in vacuo. Preparative layer chromatography [silica gel, 5% ethyl acetate petroleum ether (60-80^o C) as developing solvent] of the residue gave 25 (237 mg, 88%). IR (film) v_{max} : 2932, 2720(w), 1728, 1444, 1268, 1178, 1098, 824, 708 cm⁻¹; ¹H-NMR (200 MHz, CDCl₃): δ 9.28 (unresolvable triplet), 7.7-7.6 (m, 4H), 7.48 7.33 (m, 6H), 3.98-3.88 (m, 1H), 3.65 (s, 3H), 2.95-2.72 (m, 1H), 2.58-1.55 (m, 8H), 1.27-1.12 (m, 1H), 1.058 (s, 9H).

Methyl -2-2-[2-[(Z)-2-penteny1] -3-(tert- butyldiphenylsilyloxy) cyclopenty1] - acetate (26): To a mixture of triphenylpropylphosphonium bromide (554 mg, 1.43 mmol) and sodium hexamethyldisilazide (234 mg, 1.3 mmol) was added tetrahydrofuran (10mL) under an argon atmosphere. The mixture was stirred for 10

min at room temperature. During this period the mixture developed a bright orange colour indicating the formation of the ylide. To a solution of 25 (76 mg, 0.18 mmol) in tetrahydrofuran (4 mL) was added the solution of the ylide at -78° C during 30 min. The mixture was stirred for 1.5h at -78° C, 1h at -50° C, 1h at -30°C, 1.5h at 0°C and then the mixture allowed to attain room temperature and stirred overnight whereby the orange colour disappeared and a whitish suspension formed. This was diluted with petroleum ether (60-80° C) and the precipitated triphenylphosphine oxide separated by filtration. The filtrate was concentrated and the residue passed through a bed of silica gel. The crude oil thereby obtained was chromatographed over silica gel and eluted with ethyl acetate - petroleum ether (60-80°C) (3:97) to give 26 as a colourless thick oil (40 mg, 50%). IR (film)v_{max}: 2924, 2856, 1744, 1611, 1248, 1158, 1098, 1053, 841, 698, 611 cm⁻¹; ¹H-NMR (200 MHz, CDCl₃): δ 7.77-7.58 (m, 4H), 7.48-7.3 (m, 6H), 5.35-5.12 (m, 1H), 5.0 - 4.85 (m, 1H), 4.05-3.96 (m, 1H), 3.67 (s, 3H), 2.91-2.75 (m, 1H), 2.38 (dd, 1H, J=15 & 6.4Hz), 2.18 (dd, 1H, J=15 & 9.4Hz), 2.1-1.55 (m, 8H), 1.38-1.15 (m, 1H), 1.05 (s, 9H), 0.85 (t, 3H, J=7.5Hz).¹H-NMR for other minor diastereomer (partial): δ 4.25-4.15 (m, 1H), 2.6-2.45 (m, 1H), 0.95 (t, 3H, J=7.5Hz).¹³C-NMR (50 MHz, CDCl₃): δ 173.76 (s), 135.77 (d), 134.52 (s), 134.45 (s), 132.26 (d), 129.39 (d), 127.35 (d), 127.01 (d), 78.29 (d), 51.33 (g), 50.77 (d), 36.19 (d), 35.42 (t), 32.57 (t), 28.11 (t), 26.94 (q), 24.39 (t), 20.40 (t), 19.05 (s), 14.01 (q); ^{13}C -NMR for other minor diastereomer (partial): δ 128.21 (d), 48.45, 33.14, 28.74, 22.88.

(-)-Methyl (1R, 2S, 3S)-2[2-(Z)-2-pentenyl]-3-hydroxycyclopentyl]acetate[(-)methyl cucurbate] (2): To a solution of 26 (120 mg, 0.25 mmol) in tetrahydrofuran (5 mL) was added tetrabutylammonium fluoride trihydrate (198 mg, 0.63 mmol) under an argon atmosphere. After being stirred for 24h at room temperature, the mixture was partitioned between ether and saturated aqueous sodium chloride, and the aqueous layer was extracted with ether (3 x 15 mL). The combined ether exracts were dried (MgSO₄) and concentrated in vacuo. Preparative layer chromatography [silica gel, 15% ethyl acetate - petroleum ether (60- 80° C) as developing solvent] of the residue afforded 2 (50 mg, 84%) as a colourless oil. [α]_D = -2.03(C=1.12 in MeOH). (Lit.^{6e} [α]_D = -2.20, C = 0.22 in MeOH); IR (film)v_{max}: 3420, 2924, 2857, 1730, 1631, 1454, 1250, 1162, 1054, 689, 615 cm⁻¹; ¹H-NMR (200 MHz, CDCl₃): δ 5.5-5.2 (m, 2H), 4.06-3.83 (m, 1H), 3.67 (s, 3H), 2.8-2.45 (m, 1H), 2.40 (dd, 1H, J=15.1 & 6.3Hz), 2.14 (dd, 1H, J=15.1 & 9.3Hz), 2.11-1.85 (m, 7H), 1.62-1.52 (m, 2H), 1.4-1.2 (m, 1H), 0.98 (t, 3H, J=7.5Hz). ¹³C-NMR (50 MHz, CDCl₃): δ 173. 70 (s), 133.13 (d), 127.09 (d), 77.54 (d), 51.50 (q), 50.64 (d), 36.75 (d), 35.30 (t), 32.55 (t), 28.33 (t), 25.32 (t), 20.64 (t), 14.14 (q).

(+)-(1S, 2S, 3R) -2 -[2-[(Z) -2 -pententyl]-3- hydroxycyclopentyl]acetic acid [(+)-cucurbic acid] (6): A solution of 2 (45 mg, 0.2 mmol) in 1mL 10% aqueous methanolic potassium hydroxide was stirred overnight under an argon atmosphere at 50° C. Solvent was removed under vacuum. To the residue, 2 to 3 drops of water was added and it was acidified with 2(N) HCl. Aqueous phase was extracted with ether (3 x 10mL). The combined ether extracts were washed with brine (2mL), dried (MgSO₄) and concentrated. Column chromatography of the residue on silica gel and elution with ethyl acetate gave a colourless thick oil 6 (40 mg, 94%). $[\alpha]_D = +20.23$ (C= 0.34 in MeOH). (Lit.⁵ $[\alpha]_D = +25$, C = 0.56 in MeOH); IR (film)v_{max}: 3600, 2850, 2400, 1712, 1655, 890 cm⁻¹; ¹H-NMR (200 MHz, CDCl₃): δ 5.37 (bs), 5.52 -5.31 (m, 2H), 4.02-4.01 (m, 1H), 2.80-1.25 (m, 12 H), 0.96 (t, 3H, J= 7.5Hz); ¹³C-NMR (50 MHz, CDCl₃): δ 178.7 (s), 133.2 (d), 126.94 (d), 77.5 (d), 50.4 (d), 36.5 (d), 35.2 (t), 32.4 (t), 28.3 (t), 25.2 (t), 20.6 (t), 14.1 (q).

(+)-Methyl(1R,2S)-2-[2-[(Z)-2-pentenyl]-3-oxo-cyclopentyl]acetate[(-)-methyl epijasmonate] (1): A chromic acid solution was prepared from sodium dichromate (5.0 g, 16.8 mmol) and 95% sulfuric acid (6.93 g, 54.2 mmol) and diluted with water to make up 25 mL of total volume. To a solution of 2 (35 mg, 0.1 mmol) in ether (2.5 mL) was added chromic acid solution (0.29 mL of the stock solution) with ice-cooling. The mixture was stirred for 20 min and the top ether layer was separated and to this was added excess 2-propanol and then sodium bicarbonate at the same temperature. The mixture was filtered and washed with ether. The ether extract was washed with water, brine, dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed over silica gel and eluted with ethyl acetate - petroleum ether (60-80^o C) (1:9) to give 1 (24 mg, 69%). [α]_D = +50.4 (C = 0.96 in MeOH). (Lit.^{6c} [α]_D = +53.3, C = +0.98 in MeOH); IR (film)v_{max}: 2960, 1737, 1642, 1442, 1311, 1259, 1168, 1021, 807, 696, 616 cm⁻¹, ¹H-NMR (200 MHz, CDCl₃): δ 5.5-5.2 (m, 2H), 3.64 (s, 3H), 2.95-2.7 (m, 1H), 2.43-1.62 (m, 11H), 0.90 (t, 3H, J=7.5Hz); ¹³C-NMR (50 MHz, CDCl₃): δ 218.83 (s), 172.87 (s), 133.49 (d), 125.44 (d), 52.68 (d), 51.70 (q), 35.57 (d), 35.25 (t), 33.72 (t), 25.65 (t), 22.94 (t), 20.64 (t), 14.03 (q).

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